Candida

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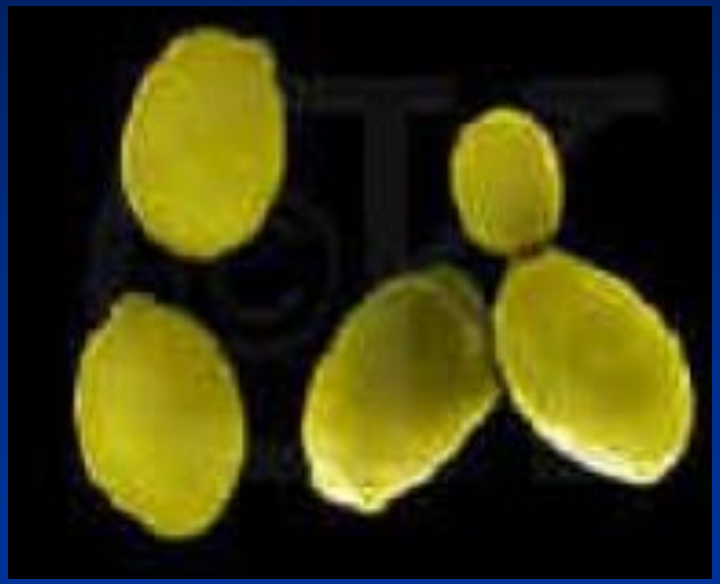
Items of the lecture

- Morphology
- Classification
- Ecology
- Candida in the environment
- Pathogenesis
- Diagnosis
- Clinical manifestations
- Treatment

Morphology

Candida are yeast-like fungi



- Small in size (4–6 μm)
- Oval in shape
- Thin-walled
- Reproduce by budding or fission

Morphology

C. albicans

- **Oval yeast**
- **2–6 × 3–9 µm in size**
- **Can produce *budding cells*, *pseudo-hyphae* and *true hyphae***

- **NB. This ability to simultaneously display several morphological forms is known as *polymorphism***

Morphology

C. albicans

NB. Although hyphae are likely to be produced during the process of tissue invasion, yeasts without hyphae may also occur in invasive disease, particularly in infections caused by non-albicans Candida species

Classification

- The genus *Candida* includes over 200 species
- Only a few species cause disease in humans

1. *C. Albicans*

2. non-*albicans Candida* species:

   They are occasional causes of human candidosis, particularly in disseminated infections.

Non-*albicans Candida* species

- *C. tropicalis*
- *C. pseudotropicalis*
- *C. krusei*
- *C. glabrata* (formerly *Torulopsis glabrata*)
- *C. dubliniensis*
- *C. parapsilosis*
- *C. guilliermondii*
- *C. lusitaniae*
- *C. zeylanoides*

Ecology

The epidemiology of candidosis is changing and, where once *C. albicans* was the predominant species isolated from clinical samples, in some countries other species are now very common.

Ecology

Commensal vs. parasite role:

1. ***Gastrointestinal tract carriage***
2. ***Vaginal carriage***
3. ***Cutaneous carriage***
4. ***Carriage in other sites***

Ecology

1. Gastrointestinal tract carriage

- *C. albicans* is a frequent normal commensal of GIT

- Colonization with *C. albicans* / another species may occur
  - during birth (directly from the birth canal),
  - during infancy *or*
  - later in life

Ecology

1. Gastrointestinal tract carriage

- Colonization of the mouth
  - **early in life** → frank pathological changes
  - **later** → usually established asymptomatically

Ecology

1. Gastrointestinal tract carriage

Oral carriage rates:

- **26%** of normal subjects carry **yeasts** in the mouth
- **C. albicans** carriage rates are about **18%**

NB. Higher figures in hospital patients

Ecology

1. Gastrointestinal tract carriage

Isolation rates of yeasts from faecal specimens / rectal swabs:

- Higher than those from oral samples
- **47%** for yeast carriage
- **41%** for *C. albicans*

Ecology

1. Gastrointestinal tract carriage

The proportion of healthy adults carrying *Candida* in GIT becomes even higher with:

1. Use of specialized isolation techniques
2. Repeated sampling
3. Administration of antibiotics effective against the resident gastrointestinal bacterial flora

Ecology

1. Gastrointestinal tract carriage

NB. The density and composition of the gastrointestinal yeast flora varies from individual to individual, and influences the chances of isolation.

Ecology

1. Gastrointestinal tract carriage

NB. Oral antibiotic therapy are likely to increase:

- incidence of carriage
- number of organisms present
- chances of tissue invasion

NB. Studies of ***Candida* serology and skin tests** suggest that a substantial proportion of those not colonized by yeasts may have been exposed to *Candida* in the past.

Ecology

2. Vaginal carriage

- The healthy vagina may be colonized by yeasts
  - most commonly → *C. albicans*
  - sometimes → *C. glabrata* (in a small proportion of women)
- Percentage of vaginal carriers
  - around 12.7% for *C. albicans*
  - higher rates in hospital patients (even without vaginal disease)

Ecology

2. Vaginal carriage

- **Factors associated with elevated carrier rates:**
  - Pregnancy
  - Oral contraceptives
  - Use of intrauterine devices

Ecology

3. Cutaneous carriage

- Generally, neither *C. albicans* nor any other species of *Candida* is a permanent member of the normal skin flora.

- Skin adjacent to the body orifices and the skin of the fingers, which are in frequent contact with the mouth, often yield *C. albicans* and sometimes other species, mainly *C. parapsilosis* and *C. guilliermondii*.

Ecology

3. Cutaneous carriage

- *Candida* may be a **persistent colonizer** of moist intertriginous sites as well as the subungual space (in patients with pre-existing nail disease).
  - **NB.** Age and climate are important in this connection.
  - **NB.** Samples from the very young and the very old are more likely to yield *Candida*.

Ecology

4. Carriage in other sites:

The bronchial tree:

- not normally colonized by *Candida*
- where the organism is isolated from sputum specimens, it can be assumed that it has come from the mouth or oropharynx.

Ecology

4. Carriage in other sites:

The bronchial tree:

- Swallowing a massive quantity of *Candida* cells → transfer of these yeasts rapidly through the gut wall into the circulation, presumably via the portal vein and the liver (***'persorption'*** of *Candida* cells)
  - occurs in normal situations ??
  - may be a portal of entry in the neutropenic patient

Candida in the environment

C. albicans can occasionally be cultured from the environment, usually in situations where there are heavily infected subjects, human or animal; for example,

- nursery (where there was an epidemic of oral thrush)
- hospital bed linen
- air of dermatology clinics (normally: *Candida* is not part of the air-borne microflora)

Candida in the environment

- Most cases of candidosis probably result from infection of the host by his or her own commensal yeasts Except for
  - **Neonatal** infections
  - **Sexual** infections

Pathogenesis

1. Fungal virulence

2. Enzymes and toxins

3. Yeast–mycelial shift

4. Adherence

5. Other factors

Pathogenesis

1. Fungal virulence

- In animal experiments, some *Candida* species have been shown to be less virulent than *C. albicans*, a finding that conforms well with clinical experience.
- Generally, the most common pathogen in skin disease is *C. albicans*, although increasingly other species are isolated in vaginal infections and from immunocompromised patients.

Pathogenesis

2. Enzymes and toxins

- Production of an acid proteinase by certain strains of *C. albicans*
- Proteinase-negative strains → less virulent

- **NB.** Laboratory-generated gene-defective strains have not been shown to be less virulent.

Pathogenesis

3. Yeast–mycelial shift

- In oral and cutaneous candidosis, scrapings examined microscopically usually show *Candida* in both budding and mycelial forms.

- In histopathology of invasive candidosis, hyphae are usually present.

This suggests that the production of hyphae may contribute to fungal virulence.

Pathogenesis

4. Adherence

- The ability of yeast forms to adhere to the underlying epithelium is essential for tissue invasion
- Adherence of *Candida* to epithelial surfaces is mediated through a number of receptor interactions
- *Candida* adhesins are based on:
  - cell wall mannan *or*
  - protein components (e.g. *Candida* surface C3d-binding protein)
- Proteinase production is necessary for adherence.

Pathogenesis

5. Other factors

Factors important in stimulating mycelium formation in experimental studies:

NB. It is difficult to relate these experimental results to the *in vivo* situation.

- Temperatures above 35°C
- Low oxygen tension
- Liquid media
- Non-sulphur-containing amino acids
- Polysaccharide carbon source
- Serum
- pH of 7.5

Pathogenesis

5. Other factors

Melanin production

Candida albicans also produces melanin, a factor known to affect resistance to immunological responses.

Pathogenesis

5. Other factors

Ecological pressures from other organisms:

Both in **GIT** and on the **skin**, removal of competing bacteria
→ increase in yeast numbers (important for invasion)

Competition between Candida and bacteria in saliva:

the amount of available glucose is a crucial factor

if elevated and plentiful (DM), the bacterial flora will not inhibit the yeast

Pathogenesis

5. Other factors

Ecological pressures from other organisms:

Mechanisms other than nutrient depletion:

- Finger web → bacteria, especially Gram-negatives, may act as co-pathogens rather than competitors, their presence enhancing the pathogenicity of the yeast
- The presence of bacteria may impair the ability of *Candida* to adhere to the underlying substrate

Host Factors
involved in mucocutaneous candidosis

- The very old, the very young and the very ill are susceptible to oral thrush

- In the mouth → carbohydrate levels are important
  - *food debris* (in the mouth of the severely ill patient with inadequate oral hygiene) may be as significant as diabetic saliva
  - *Sjögren's syndrome* → *Candida* carriage and probable susceptibility to candidosis are high (low saliva flow rates)
    - changes in pH
    - changes in IgA levels
    - simply leads to poor oral hygiene (mouth is inadequately washed by saliva)

Host Factors
involved in mucocutaneous candidosis

DM

diabetics are more susceptible to candidosis

- High glucose levels in urine, general tissue fluids and sweat.
- Impaired phagocytosis

- **NB**. In practice, infection in diabetics is largely confined to *Candida* vulvovaginitis and balanitis.

Host Factors
involved in mucocutaneous candidosis

Local tissue damage

Experimental removal of the stratum corneum →

- facilitates the establishment of cutaneous candidosis
- increases the severity of the response (increasing the availability of adhesion receptors)

In the mouth, the wearing of dentures increases susceptibility

- Trauma?
- Food debris?
- Restriction in saliva flow?

Host Factors
involved in mucocutaneous candidosis

Local tissue damage

On the skin

- maceration is essential
- in experimental candidosis, high moisture levels (provided by occlusion) are essential
- Pre-existing skin disease
  - several surveys → higher levels of *Candida* carriage on psoriatic and eczematous skin
  - one other study → *Candida* paronychia is more common in psoriatics
  - However, in general, candidosis is not a common complication of psoriasis or eczema
  - *Candida* does not colonize such diseased skin without prior removal of the bacteria

Mycological Identification of Candida (Laboratory Diagnosis)

1. Microscopic examination
2. Culture
3. Other tests (physiological tests)

Mycological Identification of Candida (Laboratory Diagnosis)

1. Microscopic examination:

Direct examination of skin or nail material ⟹ Oval thin-walled yeasts bud on a narrow base

- Usually accompanied by filaments (true hyphae or pseudo-hyphae)
- Filaments may be absent occasionally (particularly when a non-*albicans* yeast is present)

Mycological Identification of Candida (Laboratory Diagnosis)

- **NB**. The size and shape of the yeasts may suggest a non-*albicans* yeast e.g. ***C. krusei*** → budding cells are larger & more elongate than *C. albicans*

Laboratory diagnosis

- Isolation and identification of *C. albicans* is simple
- at 37°C
- on media free of cycloheximide
- swabs & skin samples
- colonies appear within 1–3 days.
- growth from thicker skin and nail material → slower (plates should be held for a week before reporting as negative)

Laboratory diagnosis

Chromogenic agars

- Allow the identification of *C. albicans* on primary culture
- On Albicans ID® agar (bioMerieux), the colonies of *C. albicans* are blue and all other yeasts cream or white
- On Chromagar® (Becton and Dickinson), colonies of *C. albicans*, *C. tropicalis* and *C. krusei* are green, blue and pink, respectively
- NB. The use of these media alone may not be reliable for differentiating species

Laboratory diagnosis

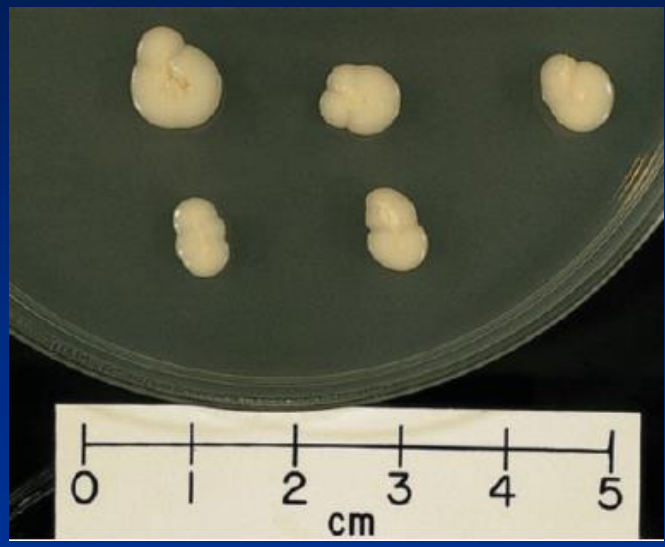
- As *C. albicans* is a common commensal, the interpretation of cultural findings has to be related to the clinical appearances. A scanty growth of *C. albicans* from the skin or from a mucocutaneous site may be meaningless without evidence of infection from a positive direct microscopy.

Laboratory diagnosis

Candida albicans

Colonies

on glucose–peptone agar →



- white to cream
- soft in texture
- some isolates may produce wrinkled ‘rough’ colonies
- some may produce an obvious fringe of pseudohyphae around the edge of the colony

Laboratory diagnosis

Candida albicans

Colonies

on depleted media → e.g. cornmeal agar or rice extract agar

- Shows the production of filaments best
- In addition to filaments and budding yeasts, *C. albicans* produces rounded ***refractile vesicles*** (erroneously termed **chlamydospores**)
  - 8–12 µm diameter at the sides and ends of the filaments
  - Produced within 24–96 h of incubation at 26°C.

Laboratory diagnosis

Candida albicans

<u>Colonies</u> on depleted media → e.g. cornmeal agar or rice extract agar

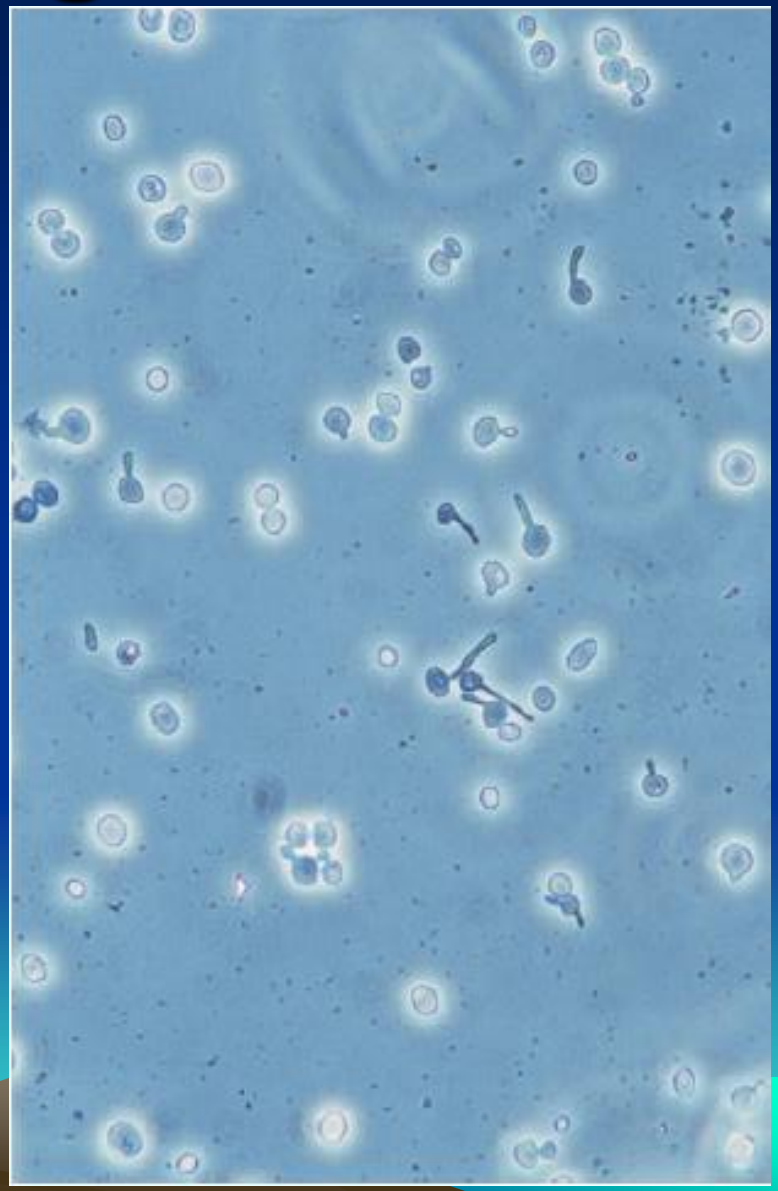
Laboratory diagnosis

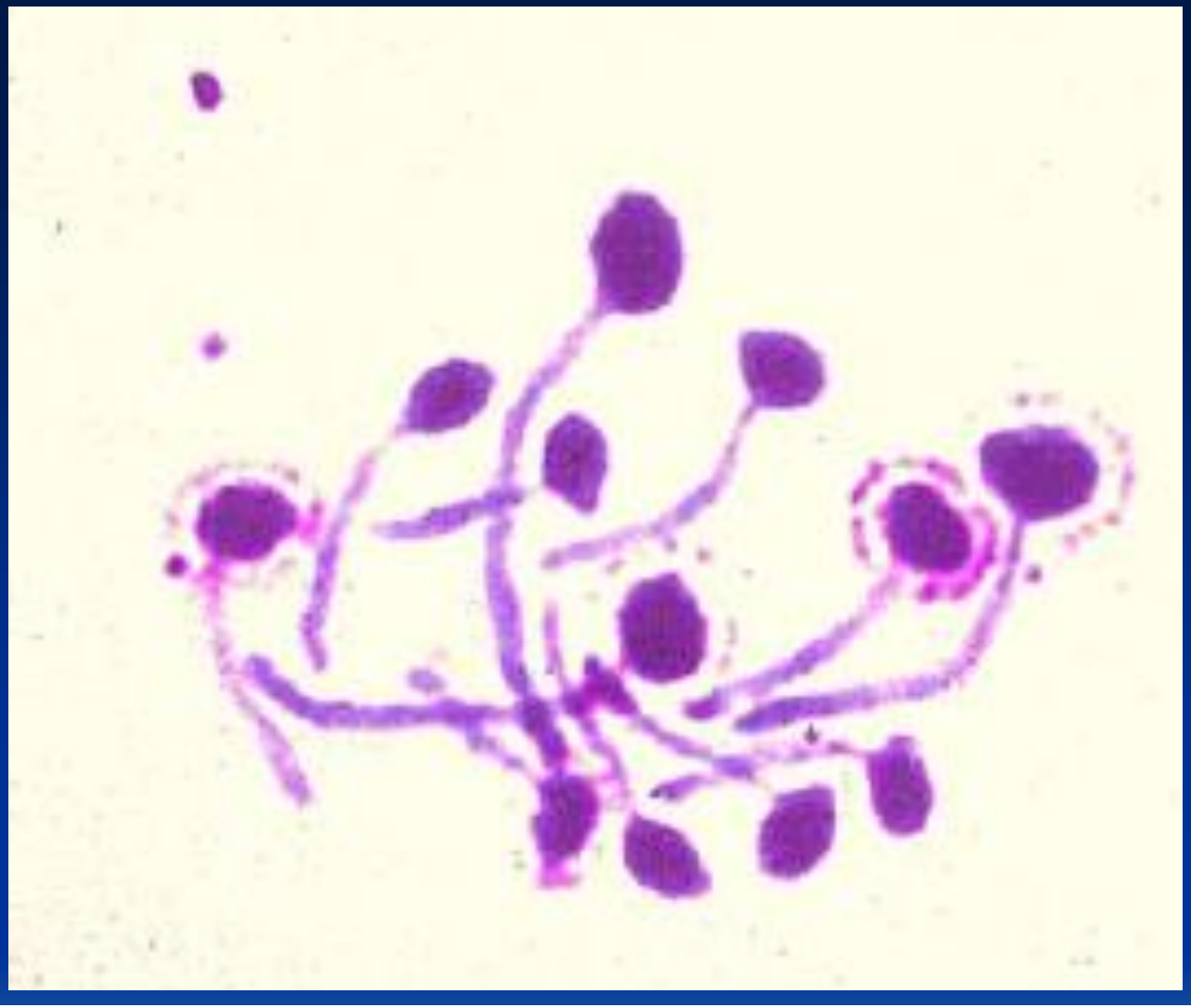
Candida albicans

Colonies

light inoculation into serum

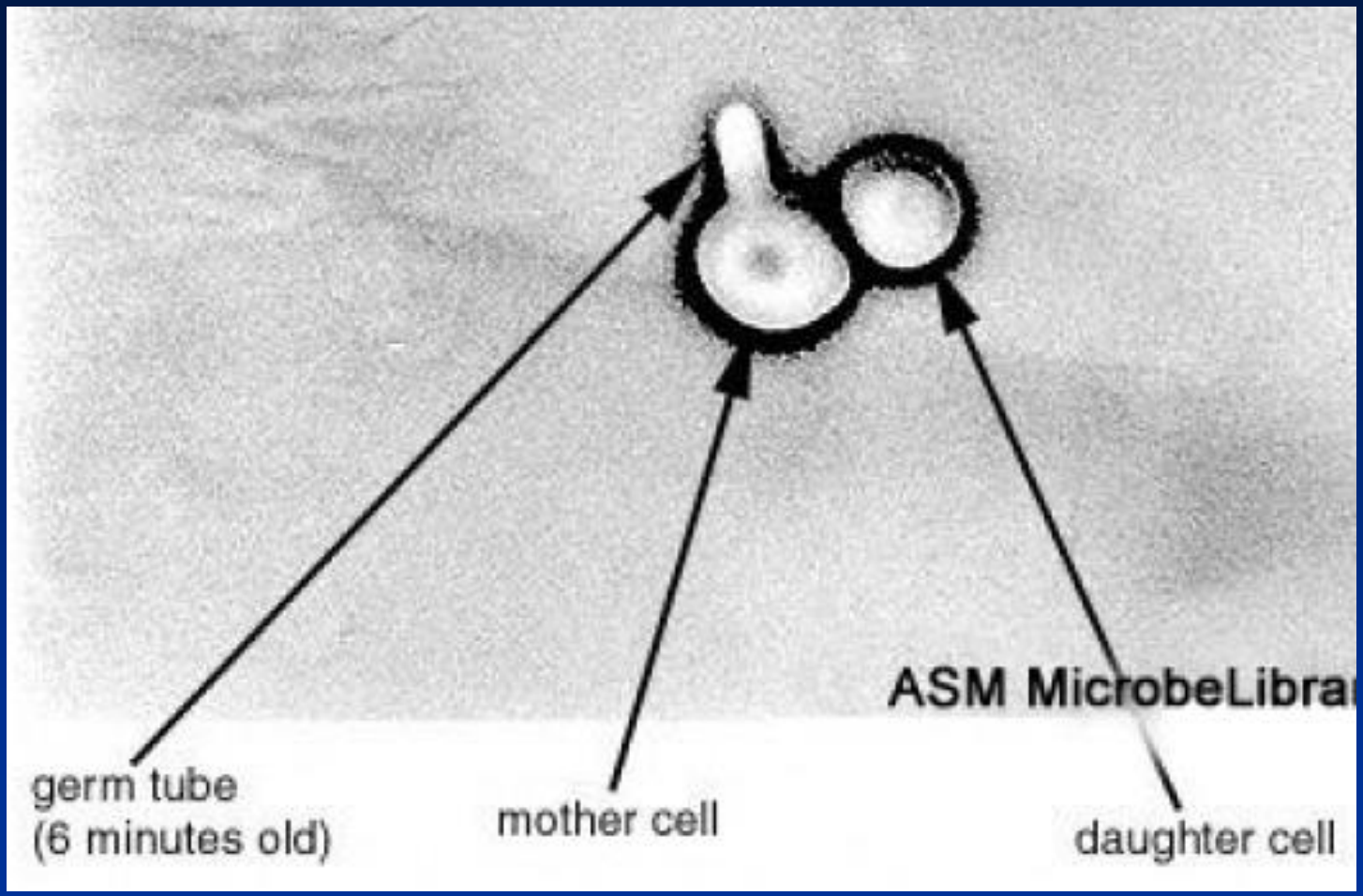
- incubated at 37°C for 2–4 h
- production of rudimentary true hyphae **"germ tubes"**
- The only other species that is germ-tube positive and produces vesicles on depleted media is ***C. dubliniensis***, a yeast associated predominantly with *oral infections* in *HIV*-positive patients.



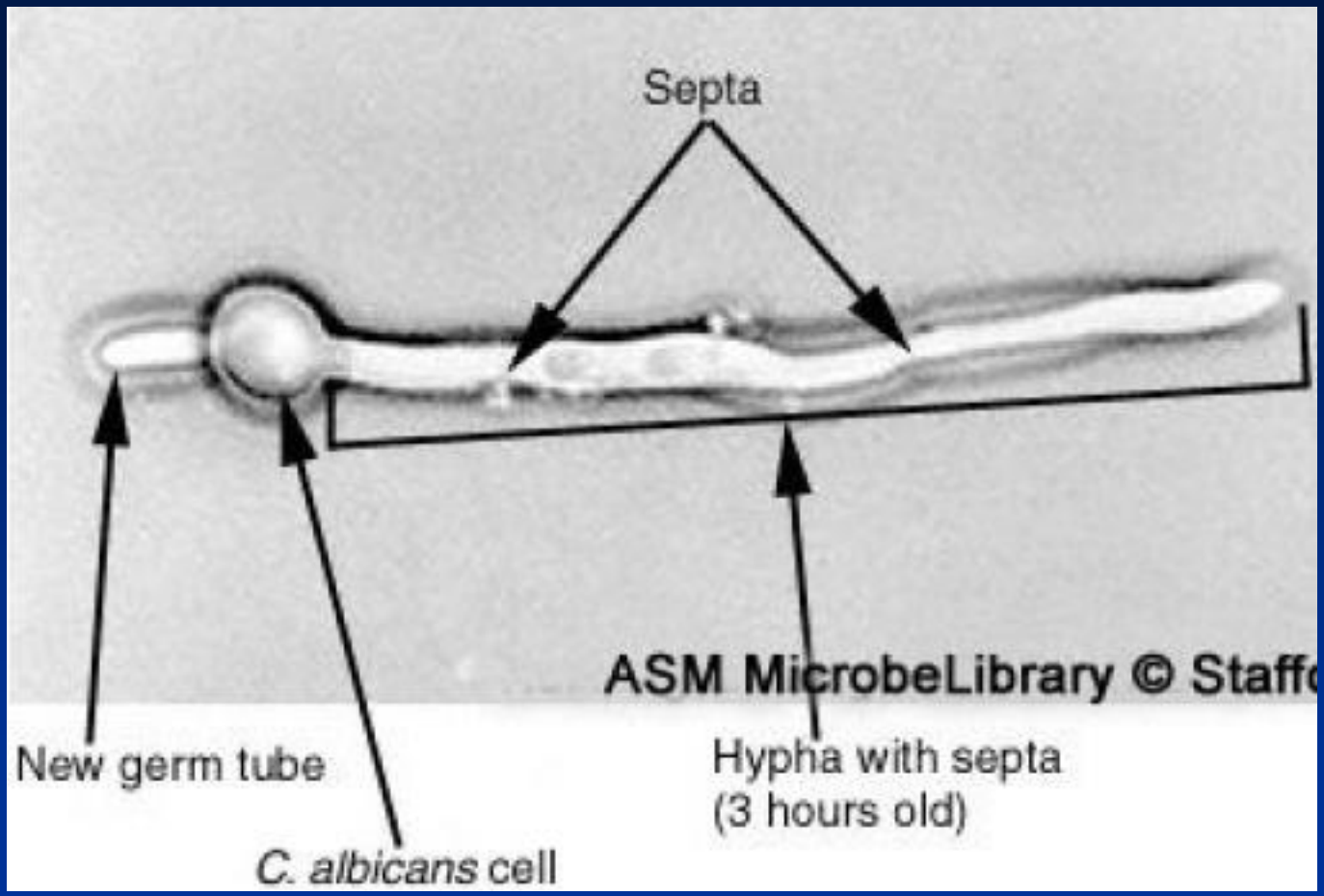


C. albicans showing germ tube production in serum “Gram stain”

C. albicans showing germ tubes. Calcofluor white stain in peptone medium.



C. albicans mother & daughter cells grown under conditions that induce hypha formation for 30 min. Daughter cell has not reached a threshold volume to form a hypha. Mother cell passed the threshold volume & started forming a germ tube (6 min old) which will become a hypha. A septum between germ tube & mother cell not formed yet. Unstained cells (x1,000 phase-contrast microscopy).



C. albicans cell 3 h after the appearance of the germ tube, the hypha has septa. A new germ tube at the distal pole of the cell is also evident at this time. The unstained cells are magnified x1,000 using phase-contrast microscopy.

Laboratory diagnosis

Microscopy (from culture):

- mounts from primary culture plates will reveal predominantly budding yeast cells.

Laboratory diagnosis

Other Candida species

Colonies

- Colonies vary slightly in texture, colour and production of obvious pseudohyphae.
- With experience, these differences may be recognized on the primary culture plates, **but** specific identification always requires study both of the morphology and physiology of each isolate.

Laboratory diagnosis

Other Candida species

Microscopy

- the majority of pathogenic *Candida* species will produce filaments and budding yeasts, but not chlamydospores, on depleted media (*C. glabrata* is a notable exception)
- the appearance of these filaments and yeasts is subtly different and characteristic for each species
- presence or absence of filaments is a key characteristic that is necessary for the identification of all *Candida* yeasts

Laboratory diagnosis

Other Candida species

Physiological tests: e.g.

- sugar and nitrogen source assimilations
- determination of the presence or absence of urease
- commercial yeast identification systems (Kits) e.g.
  - API 32C® (bioMerieux)
  - Auxacolour® (Sanofi)

Laboratory diagnosis

Other Candida species

Clinical significance of identification:

It is important to speciate non-*albicans* yeasts, because some species may show innate resistance to some antifungals; e.g., *C. glabrata* and *C. krusei* are often resistant to fluconazole.

Clinical Manifestations

Infection with candida is called:

- ***Candidosis***
- ***Candidiasis***
- ***Moniliasis***
- ***Thrush***

Clinical manifestations of candida infection falls in 3 main groups

I. **Oral** Candidosis
II. Candidosis of the **skin & genital mucous membranes**
III. Candida **paronychia**

Clinical Manifestations

I. Oral Candidosis

Acute
- Pseudo-membranous
- Erythematous (atrophic)

Chronic
- Pseudo-membranous
- Erythematous (atrophic)
- Plaque-like (hyperplastic)
- Nodular

Others
- Angular cheilitis
- Median rhomboid glossitis

I. Oral candidosis
(A) Acute candidiasis

1. **Oral thrush** (Acute **pseudo-membranous** candidosis / candidiasis)

thrush on the lips and tongue

I. Oral candidosis
(A) Acute candidiasis

2. Acute erythematous (atrophic) oral candidiasis = *'antibiotic sore tongue'*

- Marked soreness & denuded atrophic erythematous MM esp. on dorsum of the tongue
- Associated with:
  - antibiotic therapy (mainly)
  - HIV-positive subjects
  - Patients taking inhaled steroids

I. Oral candidosis
(B) Chronic candidiasis

1. **Chronic pseudo-membranous candidosis**

- As acute pseudo-membranous variety but very persistent
- Occurs mainly in immuno-compromised patients

I. Oral candidosis
(B) Chronic candidiasis

2. Chronic erythematous / atrophic candidiasis (denture sore mouth; denture stomatitis)

- Soreness in the epithelium in the denture-bearing area
- May occur in children wearing orthodontic appliances
- The affected MMs show red or dusky erythema.
- The epithelium is often shiny and atrophic

I. Oral candidosis
(B) Chronic candidiasis

3. Chronic plaque-like / hyperplastic candidiasis (Candida leukoplakia)

- Very persistent, firm, irregular white plaques on the cheek or the tongue.
- Mild symptoms (slight soreness and roughness)
- This plaque cannot be easily removed.
- ***Clinical significance:*** must be differentiated from other types of leukoplakia

I. Oral candidosis
(B) Chronic candidiasis

4. Chronic nodular candidosis

- Rare form
- Usually affects the tongue (**cobbled appearance**)

I. Oral candidosis
(C) Others

1. **Angular cheilitis (angular stomatitis; perleche)**

- Soreness at the angles of the mouth extending outwards in the folds of the facial skin
- The yeasts involved clearly come from the mouth
- Oral cavity should be examined carefully & swabs taken to establish the presence of *Candida* carriage

I. Oral candidosis
(C) Others

2. Median rhomboid glossitis

- Diamond-shaped area on dorsum of the tongue with *loss of papillae*
- It has been regarded in the past as developmental abnormality
- Current opinion suggests that it is a variant of chronic plaque-like candidosis

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

Most cases of cutaneous candidosis occur in:

- Skin folds or where there is occlusion (clothing / medical dressings) → moisturing
- Areas close to the body orifices
- Fingers (frequently contaminated with saliva)

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

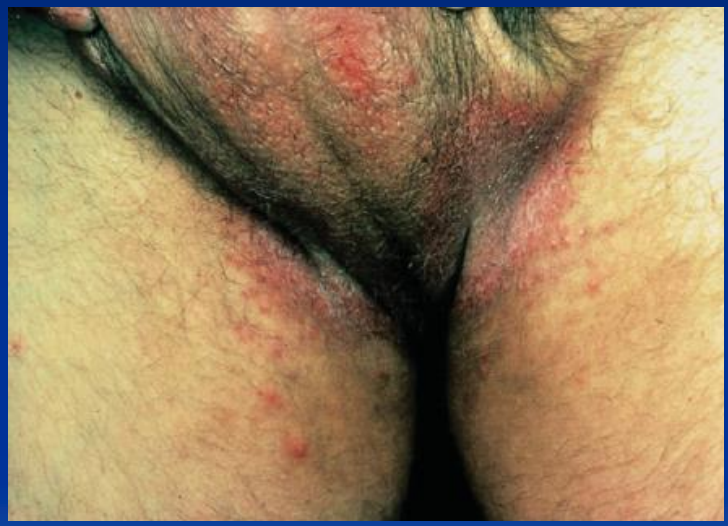
Clinical variants:

1. Candida intertrigo (flexural candidosis)
2. Vulvovaginitis (vulvovaginal thrush)
3. Candida balanitis
4. Perianal and scrotal candidosis
5. Napkin candidosis (diaper candidiasis)
6. Granuloma gluteale infantum (nodular or granulomatous candidosis of the napkin area)

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

1. Candida intertrigo (flexural candidosis)



- Any skin fold may be affected
- More common in the obese
- Erythema starting deep in the fold → spreads with a fringed irregular edge & sub-corneal pustules rupturing → tiny erosions

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

1. Candida intertrigo (flexural candidosis)

NB. Affection of **web spaces (toes or fingers):** marked maceration with a thick, white, horny layer

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

2. Vulvo-vaginitis (vulvovaginal thrush)

- This condition affects around 75% of women of child-bearing age
- Presents with itching, soreness, and thick creamy white discharge
- It is more common in pregnancy

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

3. *Candida* balanitis

- The skin of glans penis in the uncircumcised may be colonized by *Candida* asymptomatically
- When *Candida* balanitis develops, it is usual to find vaginal *Candida* carriage or vulvovaginitis in the sexual partner
- **Clinically:** transient tiny papules or pustules on the glans a few hours after intercourse with a little soreness and irritation.

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

4. Perianal and scrotal candidosis

- May occur with / without genital involvement
- Starts with non-specific erythema, soreness and irritation with classical features developing as it extends

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

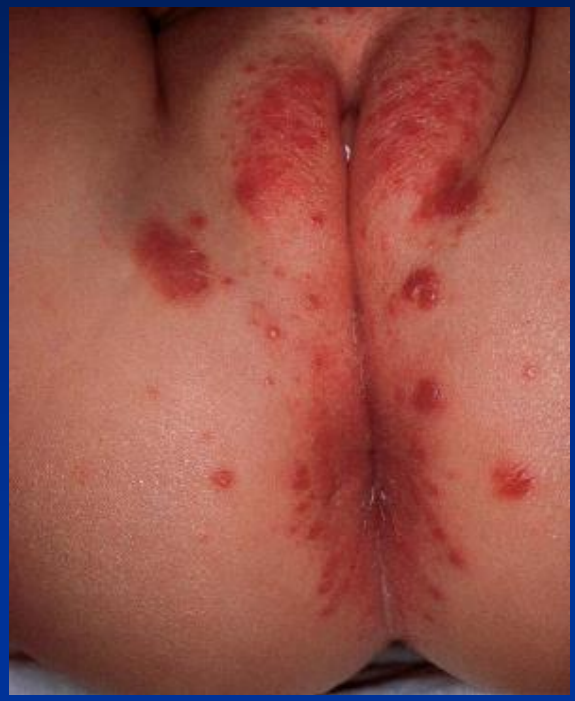
5. Napkin candidosis (diaper candidiasis)

- Affects the moist skin of the buttocks and genitalia of the infant
- More prevalent where the skin is affected by napkin rash
- Classical subcorneal pustules with a fringed irregular border and satellite lesions

Clinical Manifestations

II. Candidosis of the *skin* & *genital mucous membranes*

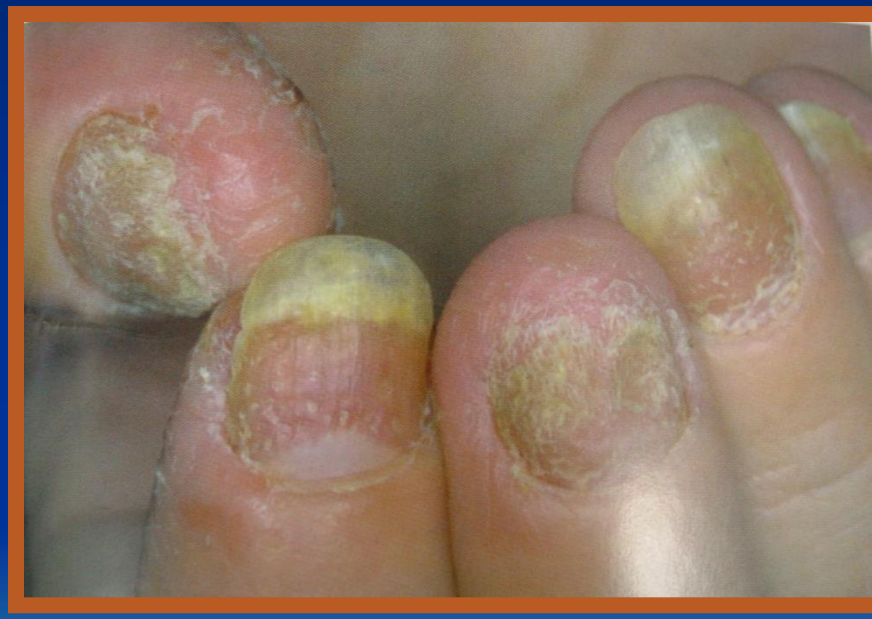
6. Granuloma gluteale infantum (nodular or granulomatous candidosis of the napkin area)



- Rare condition
- Affects the buttocks, genitalia, upper thighs and pubis
- **Nodules** (may be as large as 2 cm across), bluish or brownish in colour (reminiscent of **Kaposi's sarcoma**) ± marked scaling and hyperkeratosis
- Complicates primary napkin dermatitis
- Histologically: intense dermal infiltrate with lymphocytes, eosinophils and histiocytes.

Clinical Manifestations
III. Candida paronychia

- Mainly affects those whose hands are frequently immersed in water specially with the presence of organic debris as flour / other carbohydrates (chefs and pastry cooks)



Treatment

General principles

Removal of predisposing factors e.g.

- in the mouth: good hygiene
- in the skin: careful drying

Treatment

Therapeutic agents

The following antifungal agents are effective against candida

1. **Polyene antibiotics: Nystatin** (effective against *Candida* species and most other yeast pathogens)
2. **Imidazoles: Clotrimazole, miconazole and econazole** (the best known in topical use)
3. **Triazoles: fluconazole and itraconazole** (the most useful treatments)
4. New azoles active against *Candida* species: **voriconazole and posaconazole** (used for severe oropharyngeal and oesophageal infection)
5. **Caspofungin:** IV fungal cell wall inhibitor

Treatment

- New azoles active against *Candida* species: voriconazole and posaconazole (used for severe oropharyngeal and oesophageal infection)
- Caspofungin: IV fungal cell wall inhibitor